REMARKS

The Claim Amendments:

Claims 1-33 are currently under consideration.

Claims 1-21 and 31-33 stand allowed. Examiner has rejoined claims 22-30. Claims 22-30 stand rejected.

Applicants have amended claim 22 to recite the following diseases: osteoarthritis, pancreatitis, rheumatoid arthritis, chronic active hepatitis, inflammatory bowel disease, Crohn's disease, psoriasis, organ transplant rejection, sepsis, septic shock, cerebral ischemia, stroke, myocardial ischemia, myocardial infarction, amyotrophic lateral sclerosis, multiple sclerosis, hepatitis-B, hepatitis-C, hepatitis-G, and liver disease. Support for this amendment can be found throughout the specification as originally filed, (e.g., page 29, paragraph [0091] to page 30, paragraph [0092]; page 4, [0010]).

Applicants have canceled claims 23-26 and 29.

Applicants have amended claim 28 to depend from claim 27.

All of these amendments and cancellations are without prejudice to applicants seeking patents for the subject matter of the cancelled claims or to the non-elected subject matter.

These amendments add no new matter.

The Rejections:

1. 35 U.S.C. §112, first paragraph

Claims 22-30 stand rejected under 35 U.S.C. §112, first paragraph as failing to comply with the enablement requirement. The Examiner contends that "[t]he claims contain subject matter, which was not described in the specification in such a way as to enable one of skill in the art . . . to make and/or use the invention."

Applicants have canceled claims 23-26 and 29 and have amended claim 22 to recite an amended list of diseases. Applicants respectfully submit that the amended claims are

enabled. Applicants have submitted herewith Exhibits 1-26 to support the following arguments.

First, applicant submits that claims 27 and 28 are not directed towards the treatment of a disease, but instead are directed towards methods of cell preservation (claim 27), and methods of cell preservation as applied to organ transplant and blood (claim 28). Schierle et al. demonstrated the link between caspase inhibitors and cell preservation by showing that treatment of embryonic nigral cells with a caspase inhibitor reduced apoptosis in transplants.[1] Caspase inhibition also increased survival of dopaminergic neurons grafted into hemiparkinsonian rats. By reducing apoptosis in donor tissue, caspase inhibitors prolonged the life of implanted or grafted tissue.

Additionally, Idun Pharmaceuticals, in an October 8, 2003 press release, announced plans to move their caspase inhibitor IDN-6556 into Phase II studies for liver cell damage caused by apoptosis during liver transplants.[2] Accordingly, applicants submit that claims 27 and 28 are indeed enabled for cell preservation and methods of cell preservation as applied to organ transplant and blood.

Additionally, applicants respectfully disagree that applicants' compounds could not be used to treat the amended list of recited diseases. As set forth in applicants' specification, caspase inhibition had been linked to the treatment of the claimed diseases at the time of applicants' filing date (see, e.g., specification at page 4, paragraph [0010]). These links continue to be confirmed.

Applicants will demonstrate that a link exists between each of the claimed diseases and caspase inhibition. For each of applicants' claimed diseases, there is animal model data to support a link between caspase inhibition and the disease. Furthermore, in several cases, there is also clinical data to support this link. Accordingly, applicants respectfully

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[1] Schierle et al., in Nature Medicine, 1999, 5(1): 97-100 (Exhibit 1)

[2] Press Release for Idun Pharmaceuticals issued on 10/08/2003 (Exhibit 2).

submit that they are entitled to the claims directed to the treatment of the diseases recited in claim 22.

Caspase inhibitors have been shown to treat sepsis and septic shock in clinically relevant mouse models. Hotchkiss RS et al., by using a mouse cecal ligation and puncture (CLP) model of sepsis, showed that selective caspase-3 inhibitors and poly-caspase inhibitors prevented lymphocyte apoptosis (which is induced by sepsis) and improved survival in mice.[3]

Grobmyer et al. demonstrated that two novel caspase inhibitors rescued mice from lethal endotoxic shock in a murine model of endotoxic shock.[4] Additionally, Vertex Pharmaceuticals, in a January 8, 2002 press release, announced that it had "advanced VX-799, a potent small molecule caspase inhibitor, into development as a potential treatment for sepsis, a life-threatening infection of the bloodstream." [5] According to the press release, Vertex was "conducting a range of preclinical studies with VX-799 in preparation for clinical trials."

Caspase inhibitors have been shown to be effective at treating rheumatoid arthritis in animal models. Ku demonstrated that an ICE inhibitor that reduced IL-1ß levels *in vivo* significantly reduced inflammation in mice with collagen- or LPS-induced arthritis, an accepted animal model for rheumatoid arthritis in humans.[6]

Furthermore, Vertex Pharmaceuticals, in an SEC 10-K filing for 2002, stated that its partner, Aventis, had completed a phase IIa clinical study of pralnacasan, a small molecule ICE/caspase-1 inhibitor, in a 285 patient phase II clinical trial for rheumatoid arthritis. Vertex also announced that it had begun a Phase II proof-of-concept study

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[3] Hotchkiss RS, et al., Caspase inhibitors improve survival in sepsis: a critical role of the lymphocyte. Nature Immunol. 1, pp. 496-501 (2000) (Exhibit 3)

[4] S.R. Grobmyer et al., "Peptidomimetic Fluoromethylketone Rescues Mice from Lethal Endotoxic Shock", Molecular Medicine, 5, pp. 585-594 (1999) (Exhibit 4)

[5] Vertex Pharmaceuticals, Inc. January 8, 2002 Press Release (2002) (Exhibit 5)

[6] Ku, G. et al., "Interleukin-1β Converting Enzyme Inhibition Blocks Progression of Type II Collagen-Induced Arthritis in Mice," Cytokine, 8, pp. 377-386 (1996) (Exhibit 6).

of pralnacasan for osteoarthritis.[7] Recently completed Phase IIa studies with pralnacasan in human patients showed a dose-dependent trend towards improvement in signs and symptoms of disease as measured by ACR20 response rates after 12 weeks.

Caspase inhibitors have also been shown to treat liver injuries, including injuries associated with hepatitis based in mouse models. Rouquet described an ICE inhibitor that was effective in reducing *in vivo* liver apoptosis in mice.[8] Rouquet found that pre-treatment of mice with ICE inhibitor YVADcmk protected them from liver failure induced by injection of TNF-*a*. Rouquet also found that YVADcmk administration was highly effective in rescuing mice pretreated with anti-Fas antibody, which causes hepatic apoptosis, from rapid death, despite extensive hepatic apoptosis.

Additionally, Idun Pharmaceuticals, in a January 31, 2002 press release, announced plans to move IDN-6556, a small molecule caspase inhibitor, forward into Phase II clinical trials to determine whether IDN-6556 could decrease the liver damage that occurs from hepatitis, an inflammation of the liver, which can be caused by HCV infection.[9]

Caspase inhibitors have been shown to be effective at reducing the severity and mortality of induced pancreatitis in rats.[10] Norman demonstrated, in a rat model of pancreatitis, that animals treated with the ICE inhibitor VE-13045, a novel, irreversible peptidyl ICE inhibitor, had a mortality rate of 22% as compared to a mortality rate of 68% for untreated animals. Moreover, animals receiving the ICE inhibitor exhibited significantly less severe pancreatitis. Norman concluded that "[t]he current series of experiments demonstrates the efficacy of VE-13045 in antagonizing ICE *in vivo* and confirms the importance of ICE in the processing and secretion of IL-1" (Norman pp. 116-117). Norman's study

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[7] Vertex Pharmaceuticals Form 10-K for 2002, p. 12. (Exhibit 7)

[8] Rouquet, N. et al., "ICE Inhibitor YVADcmk is a Potent Therapeutic Agent Against *In Vivo* Liver Apoptosis," Curr. Biol., 6, pp. 1192-1195 (1996) (Exhibit 8).

[9] PRNewswire Press Release for Idun Pharmaceuticals issued on 01/31/2002 (Exhibit 9).

further demonstrates the profound detrimental effect of IL-1ß during acute pancreatitis and therapeutic applications of ICE blocked in this disease.

Caspase inhibitors have been shown to be effective in the treatment of stroke and other CNS injuries. Specifically, *in vivo* inhibitory effects of ICE have been demonstrated via an apoptotic pathway. Endres showed that ICE inhibitor z-VAD.FMK exhibited neuroprotective effects in a mouse model of mild ischemia.[11] Endres demonstrated that mice treated with 120 ng of z-VAD.FMK 6 hours after reperfusion decreased infarct size and neurologic deficits at 72 hours, and sustained these protective effects for at least 7 days (Endres p. 242).

Cheng also demonstrated that delayed administration of a caspase inhibitor after hypoxic-ischemic brain injury in rats resulted in significant neuroprotection. For example, Cheng showed that rats treated with BAF (a pan-caspase inhibitor) were protected against > 50% tissue loss in the cortex, the hippocampus, and the straitum compared with rats treated with vehicle only.[12]

Caspase inhibitors have been shown to be effective at treating traumatic brain injury in an animal model. Knoblach showed activated and caspase3- and caspase-9 activity in rats following lateral fluid-percussion traumatic brain injury ("TBI").[13] Knoblach also demonstrated that administration of a broad caspase inhibitor 15 minutes after TBI "improved motor and cognitive neurological dysfunction after [traumatic brain injury]" in rats (Knoblach p. 1168). The injured animals performed better than control animals in motor and spatial learning tests (see page 1161).

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[10] Norman, J. et al., "Severity and Mortality of Experimental Pancreatitis are Dependent on Interleukin-1 Converting Enzyme (ICE)," J. Interferon Cytokine Res., 17, pp. 113-118 (1997) (Exhibit 10).

[11] Endres, M. et al., "Attenuation of Delayed Neuronal Death After Mild Focal Ischemia in Mice by Inhibition of the Caspase Family," J. Cereb. Blood Flow and Metab., 18, pp. 238-247 (1998) (Exhibit 11).

[12] Y. Cheng et al., "Caspase Inhibitor Affords Neuroprotection with Delayed Administration in a Rat Model of Neonatal Hypoxic-Ischemic Brain Injury", Journal of Clinical Investigation, 101 (9), pp. 1992-1999 (1998); (Exhibit 12).

[13] Knoblach, S.M. et al., "Multiple Caspases are Activated after Traumatic Brain Injury: Evidence for Involvement in Functional Outcome," J. Neurotrauma, 19, pp. 1155-1170 (2002) (Exhibit 13).

Caspase inhibitors have been shown to be effective at treating myocardial infarction and ischemia in animal models. Yaoita showed that ZVAD-fmk, an ICE-like inhibitor, was effective in reducing myocardial reperfusion injury in a rat model, which could be at least partially attributed to the attenuation of cardiomyocyte apoptosis.[14]

Additionally, Idun Pharmaceuticals, in a February 5, 2002 press release, announced plans to move their small molecule caspase inhibitor IND-6734 into Phase I studies in human patients for myocardial infarct.[15] The decision was based on positive results in rodents where "IDN-6734 decreased heart muscle damage by 27% to 55% when administered after a simulated heart attack" and in pigs where IDN-6734 "provided a 22% to 32% reduction in heart muscle damage." The result in pigs was noted as a significant step in the decision to enter human clinical trials because of the similarity in response to injury and therapeutic treatment between pig and human hearts.

Caspase inhibitors have been shown to be effective at treating psoriasis in animal models. Vertex Pharmaceuticals, in their SEC 10-K filing for 2002, stated that VX-765, a caspase inhibitor, reduced inflammation and cytokine levels in an animal model for dermatitis.[16] Antonopoulos showed that a caspase-1 peptide inhibitor potently inhibited epidermal LC migration, the first step in skin immune response.[17]

Additionally, Vertex Pharmaceuticals, in a press release dated October 4, 2005, announced that it had completed dosing in a four-week, Phase IIa safety and pharmacokinetic study with VX-765, a caspase inhibitor, in 68 patients with psoriasis.[18]

Caspase inhibitors have been shown to be effective at treating inflammatory bowel disease in a colitis animal model.

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[14] Yaoita, H. et al., "Attenuation of Ischemia/Reperfusion Injury in Rats by a Caspase Inhibitor," Circulation, 97, pp. 276-281 (1998) (Exhibit 14).
[15] PRNewswire Press Release for Idun Pharmaceuticals issued on 02/05/2002 (Exhibit 15)
[16] Vertex Pharmaceuticals Form 10-K for 2002, pp. 6-7. (Exhibit 16).
[17] Antonopoulos C, Cumberbatch M, Dearman RJ et al. Functional caspase-1 is required for Langerhans cell migration and optimal contact sensitization in mice. J Immunol 2001; 166: 3672-7. (Exhibit 17).
[18] Vertex Pharmaceuticals Inc. October 4, 2005 Press Release (Exhibit 18)

Loher et al. demonstrated that the ICE inhibitor pralnacasan reduced dextran sulfate sodium induced murine colitis and T helper 1 T-cell activation.[19] Siegmund stated in his review article that activation of ICE occurs during different types of infectious colitis, and "ICE expression and subsequent release of IL-1ß and IL-18 significantly contribute to intestinal inflammation."[20] Siegmund also stated that ICE knockout mice as well as mice treated with the ICE inhibitor pranalcasan were protected against experimental mucosal inflammation.

Caspase inhibitors have been shown to be effective at treating multiple sclerosis in animal models.[21] Furlan showed that caspase-1 deficient mice and mice treated with a caspase-1 inhibitor showed lower experimental autoimmune encephalomyelitis, a mouse model for multiple sclerosis.[22] Caspase-1 levels have also been shown to be elevated in the brains of humans that had multiple sclerosis.[23] Furthermore, in a human cell line that is relevant to multiple sclerosis, a caspase inhibitor "was able to block the cytotoxic effects of TNF-a/IL-1ß in a dose-dependent manner" (Furlan p. 17).

Caspase inhibitors have been shown to be effective at treating amyotrophic lateral sclerosis (ALS) in animal models.[24] Li showed that a broad caspase inhibitor demonstrated "inhibition of disease progression and extended survival in a transgenic mouse model of ALS" (Li p. 338).

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[19] Loher, F. et al., The interleukin-1beta-converting enzyme inhibitor pralnacasan reduces dextran sulfate sodium-induced murine colitis and T helper 1 T-cell activation. J. Pharmacol. Exper. Therap. 308, pp. 583-590 ((2004); (Exhibit 19).

[20] Siegmund, B., "Interleukin-1ß Converting Enzyme (Caspase-1) in Intestinal Inflammation," Biochem. Pharmacol., 64, pp. 1-8 (2002). (Exhibit 20)

[21] Ahmed, Z. et al., "A Role for Caspase-1 and –3 in the Pathology of Experimental Allergic Encephalomyelitis," Am. J. Path., 161, pp. 1577-1586 (2002) (Exhibit 21).

[22] Furlan, R. et al., "Caspase-1 Regulates the Inflammatory Process Leading to Autoimmune Demyelination," J. Immunol., 163, pp. 2403-2409 (1999) (Exhibit 22).

[23] Ming, X. et al., "Caspase-1 Expression in Multiple Sclerosis Plaques and Cultured Glial Cells," J. Neurol. Sci., 197, pp. 9-18 (2002) (Exhibit 23).

[24] Li, M. et al., "Functional Role of Caspase-1 and Caspase-3 in an ALS Transgenic Mouse Model," Science, 288, pp. 335-339 (2000) (Exhibit 24).

Friedlander showed that in a transgenic mouse model of ALC, inhibition of ICE slowed the symptomatic progression of ALS.[25] Moreover, elevated caspase levels, particularly ICE levels, have been found in human ALS patients.[26]

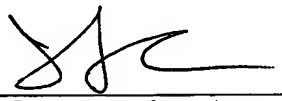
As discussed above, applicants have demonstrated that caspase inhibition is useful in the treatment of the diseases recited in claim 22. Applicants' specification coupled with the knowledge in the art at the time of applicants' filing date provide the skilled artisan with the requisite assurance, without requiring undue experimentation, that the claimed methods have the asserted utility.

For all of the reasons set forth above, applicants request that the Examiner withdraw these section 112, first paragraph rejection.

Conclusion

Applicants request that the Examiner enter the above amendments, consider the accompanying remarks, and allow the pending claims to pass to issue.

Respectfully submitted,



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[25] Friedlander, R.M. et al., "Inhibition of ICE Slows ALS in Mice" Nature, 388, pp. 31 (1997) (Exhibit 25).
[26] Ilzecka, J. et al., "Interleukin-1ß Converting Enzyme/Caspase-1 (ICE/Caspase-1) and Soluble APO-1/Fas/CD 95 Receptor in Amyotrophic Lateral Sclerosis Patients," Acta Neurolog. Scand., 103, pp. 255-258 (2001) (Exhibit 26).